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1994 - 1997	PostDoc - Institute for Biochemistry I, University of Heidelberg, Germany (Prof. Felix T. Wieland)
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Walter Nickel

Unconventional Protein Secretion

Goal

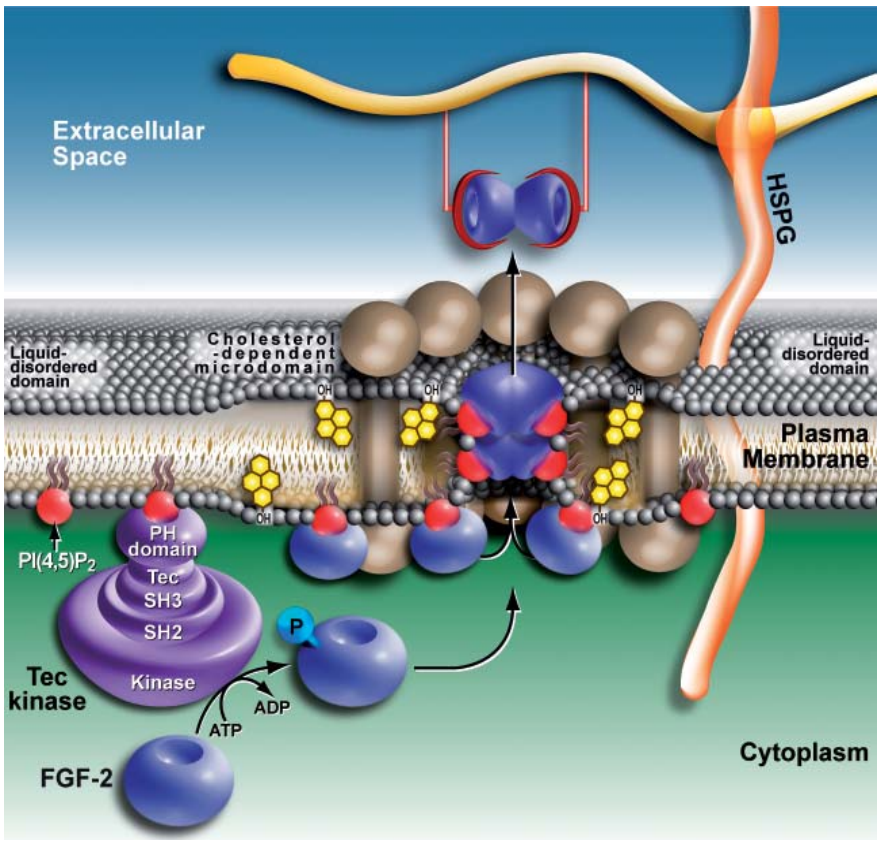
To reveal the molecular components and mechanisms involved in unconventional secretion of fibroblast growth factor 2 (FGF2), a potent mitogen mediating tumor-induced angiogenesis.

Background

The vast majority of extracellular proteins are secreted by the classical ER/Golgi-dependent secretory pathway, however, numerous exceptions have been identified. As opposed to proteins that are transported along the classical route, unconventional secretory proteins lack a signal peptide and their export from cells is not affected by brefeldin A, an inhibitor of ER to Golgi trafficking. Several kinds of unusual secretory pathways have been described some of which involve intracellular vesicles such as secretory lysosomes or multi-vesicular bodies. By contrast, unconventional secretion of FGF2 has been shown to occur by direct translocation across plasma membranes resulting in its association with heparan sulfate proteoglycans on cell surfaces. Using genome-wide RNAi screening approaches as well as biochemical reconstitution experiments, our laboratory functionally dissects molecular components and mechanisms involved in unconventional secretion of FGF2.

Research Highlights

As illustrated in Fig. 1, three critical components of the unconventional secretory machinery of FGF2 have been identified all of them being associated with plasma membranes. In addition to our earlier findings demonstrating an essential role of heparan sulfate proteoglycans that provide membrane-proximal FGF2 bindings sites on the extracellular side of the plasma membrane (Zehe et al. 2006, Proc. Natl. Acad Sci. U.S.A. 103:15479-15484), we have identified a membrane lipid, the phosphoinositide PI(4,5)P_2, that is required for the recruitment of FGF2 at the inner leaflet of plasma membranes (Temmerman et al. 2008). Based on FGF2 variant forms that fail to bind to PI(4,5)P2 and RNAi-mediated inhibition of PI(4,5)P2 biosynthesis, we demonstrated an essential role of PI(4,5)P_2 in FGF2 secretion. PI(4,5)P_2-dependent recruitment of FGF2 at the inner leaflet of plasma membranes does not only direct FGF2 into the cell periphery but also induces its oligomerization and membrane insertion (Fig. 1). In a cellular context this process is likely to be facilitated by integral membrane proteins that may form a microenvironment for example enriched in PI(4,5)P_2 and other membrane lipids favoring membrane curvature. Depending on such local properties of the plasma membrane, multivalent FGF2 oligomers may be able to penetrate and



RNAi screening including integral plasma membrane proteins, a major goal of our future work will be to reconstitute FGF2 membrane translocation in vitro using chemically defined components. In this way we aim at defining the core machinery as well as regulatory components involved in unconventional secretion of FGF2 from cells.

Fig. 1: Molecular components and mechanisms involved in FGF2 translocation across plasma membranes (Nickel, Curr Opin Biotechnol, 2010; 21(5):621-6.).

break the permeabilitry barrier of the plasma membrane resulting in membrane insertion. This model is also consistent with our finding that FGF2 translocates across plasma membranes in a fully folded conformation (Cespon-Torrado et al. 2009, J. Cell Sci.). To complete membrane translocation, on the extracellular side of the plasma membrane, heparan sulfate proteoglycans are required to extract FGF2 from the membrane resulting in its storage on cell surfaces.

Using a genome-wide RNAi screening approach, a third component of the FGF2 secretion machinery was revealed to be Tec kinase (Ebert et al., 2010), an enzyme that contains a PH domain and, alike FGF2, is recruited to the inner leaflet by phosphoinositides (Fig. 1; Nickel, 2010). FGF2 has been demonstrated a target of Tec kinase resulting in its phosphorylation at tyrosine 82. This modification is essential for FGF2 secretion and may play a role in $PI(4,5)P_2$-induced FGF2 oligomerization and membrane insertion.

Based on the components illustrated in Fig. 1 as well as additional factors identified through

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